REMARKS/ARGUMENTS

This is in response to the Office Action mailed April 7, 2008 for the above-captioned application. Applicants request an extension of time sufficient to make this paper timely, and enclose the fee.

Reconsideration of the application in view of the remarks herein is respectfully requested.

Claims 1-5, 7-9, 15, 17 and 19 are considered in this application. Claims 6, 10, 16, 18 and 20 are withdrawn.

Independent claims 1 and 7 have been amended to specify that the therapeutic agent targets and inhibits the signaling function of β4. This amendment is supported in the specification, *inter alia*, on Page 4, lines 27-30. Claim 1 has also been amended to include the limitation of claim 4 to indicate that the angiogenesis is pathological angiogenesis (see definition on Pages 7-8). Claim 7 already included such a limitation.

Applicants enclose an IDS listing additional references which are cited herein in response to the rejections made by the Examiner. Copies of the references are also enclosed.

Claims 1-5, 7-9, 15, 17 and 19 stand rejected under 35 USC § 112, first paragraph, as lacking enablement. The Examiner asserts there is no enablement of a method as in claim 1, 4 and 7 wherein the therapeutic agent targets β4, or where the agent is an antibody that targets β4. In support of this position, the Examiner makes the following assertions and arguments.

On Page 3 of the official action, the Examiner asserts that there is "no working empirical data demonstrating that the claimed anti-β4 antibody would inhibit angiogenesis." He then cites multiple references apparently to support an argument that evidence is necessary to make the operability of the invention credible. Applicants respectfully traverse this rejection.

The Examiner relies on selected parts of various references, including some that are prior art to the present application in an effort to build a case for that examples of actual inhibition of angiogenesis are necessary in the present application because a person skilled would require undue experimentation to practice the invention. Applicants understand that this is actually a challenge to the credibility of the assertion of operability in the specification since the Examiner is essentially challenging the objective truth of the statements in the specification that treatment with a therapeutic agent targeted to β4 will result in an inhibition of angiogenesis.

As a basis for this challenge, the Examiner offers an incomplete summary of the Kennel reference (note that the abstract refers to β4 expression in intermediate size vessels as well as the

vessels mentioned by the Examiner) and the Sepp reference, but never offers any explanation of how the selected teachings contribute to the argument of non-enablement. Accordingly, Applicants are unable to respond to the rejection to the extent it is based on these references. Furthermore, it is noted that these references merely look at expression patterns, i.e. the presence or absence of integrins from certain tissues. However, integrins are known to be part of complex signaling pathways, and therefore expression of integrins need not correlate with functional activity within the cell. (See Senger et al, Page 13616) Furthermore, the absence of expression at a given point in time may mean that the expression of has not yet been induced, not that it is never present. It is further noted that these studies are not looking at expression patterns in pathological angiogenesis.

The cited Nguyen article shows results concerning the role of β4 expression with respect to angiogenesis and suggests that is may cause arrest of angiogenesis. Finally, the Lipscomb reference is offered to tie it all together. However, the Lipscomb reference barely mentions angiogenesis, but rather presents results relating to the role of integrins in tumorigenesis. When it does discuss angiogenesis, Lipscomb cites to the publication based on the work disclosed in the present application and the evidence of non-universality which the examiner relies on as part of his argument is in fact disclosed in the present application. (Page 23). Neither the disclosure in the application of a limited number of negative test results, nor the subsequent publication of these results is a basis for an enablement rejection. (See MPEP § 2164.08(b)) Thus, Applicants submit that the alleged basis for finding a lack of enablement is incomplete and inaccurate, and that the rejection should therefore be withdrawn.

Notwithstanding the foregoing, Applicants would generally agree with the conclusion that **prior to the present invention** there was a lack of knowledge as to the actual role of β4 with respect to angiogenesis. In making the enablement rejection in this case, however, the Examiner is improperly considering just the extrinsic references, and fails to include the specific results in the specification in the assessment of whether the application considering **all** of the evidence provides a credible enabling disclosure. In the absence of expressly described consideration of the entire body of evidence including the results in the specification, Applicants submit that the Examiner has failed to meet the burden to present a prima facie case for lack of enablement to which Applicants are required to respond. Nevertheless, Applicants point out that the specification provides many additional experimental results, all of which support the conclusion that inhibition of the signaling functions of β4 leads to a reduction in angiogenesis.

The mice which are used in the experiments described in the present invention are not deficient in β4 as a whole but rather have a deletion in C-terminal signaling portion of the protein. (Page 15, lines 20-21). Thus, the β4 in these mice retain the adhesion functions of β4, and the experiments with the mice isolate one of the two functions of β4 for study. These two

functions, adhesion and signaling, are suggested to be temporally and functionally distinct. (See Lipscomb, Page 10970, Col. 2).

Using the mouse model, it was shown in the test results in the application that there were no macroscopic defects in the mice, indicating that β4 signaling was not required during embryonic vasculogenesis and angiogenesis. (See Page 17) This difference can in part account for the differing results in the studies relied on by the Examiner. The specification further reports that substantial amounts of α6β4 was detected in medium and large vessels of five diverse types of tumors: papillary thyroid carcinoma, prostate cancer, breast cancer and glioblastoma multiforme (See Page 17) and melanoma (Page 18). Angiogenesis in four tumor types (melanoma, Lewis lung carcinoma, lymphoma and fibrosarcoma) was shown to be reduced in mutant mice as opposed to wild type mice. (Page 23). Thus, the specification provides real evidence of the important relationship between β4 signaling and pathological angiogenesis, and this evidence is not contradicted by the cited references. As such, Applicants submit that the present application provides a fully enabling and credible disclosure and that the rejection should be withdrawn.

The Examined claims also stand rejected under 35 USC § 112, first paragraph, as lacking written description. On page 5 of the office action, the Examiner identifies 3 aspects of the claimed invention (1) tissue expressing α6β4 integrin; (2) agent that targets β4; and (3) pathological angiogenesis in a tissue expressing α6β4 integrin and states that Applicants have not provided enough examples to constitute a representative number of species nor provided a description of structural features that are common to species within each genus. Applicants respectfully disagree.

As to the term "tissue expressing α6β4 integrin" the common structural feature that is recognized in the specification and in the term itself is the structural feature of expressing α6β4 integrin. Furthermore, as to the breadth of this term and " pathological angiogenesis in a tissue expressing α6β4 integrin" the Examiner's attention is directed to the disclosure on Pages 7-8, and to the multiple tumor types tested in the experiments in the application. The assertion on Page 5 of the Office Action that a person skilled in the art is supposed to go figure out for themselves what a relevant tissue or a pathological angiogenesis in a relevant tissue looks like is specious, and assumes that the person skilled in the art has no skills at all. This is plainly in error on two counts.

With respect to the therapeutic agent, the Examiner states that "the specification fails to provide anti-β4 or RNAi that blocks activate signal transduction that can be used in the claim method." Leaving aside the fact that this sentence is not clear and appears to be inherently contradictory, Applicants direct the Examiner's attention to the disclosure of two antibodies to β4 on Pages 12-13 of the application, a specific β4 targeting oligonucleotide therapeutic agent (Seq.

ID No. 4 on Page 12), and a human integrin β4 binding protein (Seq. ID No. 1, Page 10). Furthermore, since the nature of the deletion in the C-terminal region of β4 identifies the region responsible for signaling, isolation and identification of additional therapeutic agents is within the skill in the art using ordinary and conventional techniques and techniques such as those described in the section entitled Screening Assays beginning on Page 13. Thus, Applicants submit that the rejection for lack of written description is in error and should be withdrawn.

The Examiner claims also stand rejected as anticipated by US Patent Publication No. 20030224993 or the corresponding WO02/30465. The Examiner cites these references for a disclosure of treating proliferation of various types of cancer using compositions that inhibit ligand binding to integrin β4 including antisense and antibodies. The Examiner acknowledges that there is no specific teaching concerning inhibition of angiogenesis but that this is merely a newly discovered result of a known method or statement of intended purpose that does not result in a manipulative difference. On this basis, he asserts that the claims are anticipated.

Applicants submit that the Examiner has inappropriately combined and confused legal standards relating to composition or article claims, by trying to apply them to method claims. It is certainly true that under US law, discovery of a new use for an old composition will not make that composition patentable again, even if the statement of intended use is included in the claims. The same is not the law with respect to method claims. In the case of a method claim, a showing of anticipation requires that practicing the method described in the art would inherently (i.e. necessarily) achieve the undisclosed result which it the object of the claimed method, i.e. inhibiting angiogenesis. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990)(To establish anticipation under the theory of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.") The Examiner cannot meet this requirement by ignoring it. Further, the prior disclosure must be one that places the public in possession of the invention as claimed, i.e. in possession of the knowledge that elimination/reduction of the β4 signaling will result in reduced angiogenesis. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978)(If anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accident or unwitting anticipation of an invention cannot constitute an anticipation.").

It is further pointed out that no experiments described in the '993 publication appear to be of a type that would lead to discovery of information about angiogenesis. The examples are carried out in tissue cultures. Moreover, since β4 integrin is modified through the introduction of a dominant-negative protein and not by antisense reduction in the amount of β4 it is not directly reflective of what occurs when endogenous β4 is reduced, and the observed effects could be due to any of a variety of mechanisms.

Finally, it is noted that claims 1 and 7 now require targeting of the signaling function of β4. Nothing in the cited reference discloses this element of the claims.

Thus, Applicants submit that the Examiner has applied in inappropriate legal standard and has failed to establish a prima facie case of anticipation. The rejection should therefore be withdrawn.

The examined claims are also rejected as anticipated by US 20060172957. Like the references of the previous rejection, this references makes no mention of angiogenesis, and the Examiner has applied the same erroneous logic. Furthermore, Applicants point out that this reference relates to oligonucleotide inhibitors and that there is no disclosure of using an antibody as a therapeutic agent. Accordingly, the rejection of claims 5, 9, 17 and 19 as anticipated is clearly in error.

The examined claims also stand rejected under 35 USC § 103 as obvious over Enenstein. Enenstein is a descriptive paper in which the distribution of integrins in a particular tissue type (neonatal foreskin) is observed. As stated by the Examiner, Enenstein teaches that α6 and β4 are found in capillary loops and extended to the distal ends of presumed sprouts. Enenstein also reports different distribution patterns for other integrins. The conclusion that the authors draw in the paper is that this suggests an important role for α6β4 integrin in the initial stages of endothelial outmigration. The Enenstein paper says nothing, however, about what this role might be, nothing about pathological angiogenesis, nothing about targeting any part of the α6β4 integrin as a means of inhibiting angiogenesis of any sort, nothing about targeting the signaling part of β4.

On the basis of this teaching, the Examiner asserts that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to consider blocking tube formation by anti-β4 antibodies taught by Enenstein and Kramer." This argument presupposes many things that the Examiner has not shown to be true. First it assumes that the mere expression of an integrin in a tissue is a valid basis to assume anything about its function. Certainly, the Enenstein reference makes no such supposition, and neither does the art in general. The Senger paper cited above makes this point. Furthermore, simply looking at upregulation of integrins within tumor vasculatures does not necessitate the conclusion that they are functional or necessary. This was demonstrated in the case of αVβ3 and the closely related αVβ5. αVβ3 is upregulated on certain tumor vasculatures and was thought to be important for angiogenesis but a series of papers on genetically altered mice demonstrated that neither of these integrins are necessary for angiogenesis in vivo. (Stephens 1995, Reynolds 2002, McCarty 2002, Zhu 2002, Hynes 2002). Thus, while αVβ3 may be a valid target (as reflected in the clinical trials of Vitaxin noted in the Hynes review), it is not so simply because of the expression pattern. Indeed, Hynes offers some interesting speculations to show just how complicated the system may be.

The Examiner continues on Page 8 of the office action with a statement that does not appear to be fairly based in the reference. This passage includes a statement as a given that "β4 integrin subunit[s] function in cord formation in vivo." The actual statement is the reference is much more speculative, i.e.: that "**if** integrins function in cord formation *in vivo*, one would expect that a major component would be some non-β1 integrin, such as β4." Thus, the reliance on this statement appears to be in error. Further, the Examiner refers to "the inhibition of tube formation using the anti-β4 antibodies taught by Enenstein." Applicants do not find any teaching of such inhibition by anti-β4 antibodies. Rather Page 385, Col. 1 refers to inhibition of tube formation by antibodies to α6 or β1, but not αV. There is no mention of antibodies to β4.

Given the above discussions, and the errors in the characterization of the Enenstein reference on which the rejection relies, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness. The rejection should therefore be withdrawn.

For these reason, Applicants submit that all of the claims of this application are in form for allowance. Favorable reconsideration and allowance of all claims are respectfully urged.

Respectfully submitted,

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Enclosures